

Remarks

This responds to the Office Action dated November 30, 2004. Claims 21 to 25, 27 to 31, 33, 35, 38, 39, and 41 to 45 were acted on by the Examiner. Claims 1 to 3, 5 to 9, 11, and 12 have been withdrawn. Claims 4, 10, 13 to 20, 26, 32, 34, 36, 37, and 40 have been canceled without prejudice. No claims have been amended. No claims have been added. Accordingly, claims 21 to 25, 27 to 31, 33, 35, 38, 39, and 41 to 45 are presented for examination.

Summary of the Examiner's Action**Claim Rejections**

Claims 21 to 25, 27 to 31, 33, 35, 38, 39, and 41 to 43 stand rejected under 35 U.S.C. §112, second paragraph, as failing to comply with the enablement requirement.

Claims 23 to 25 and 27 stand rejected under 35 U.S.C. §103(a) as being obvious in view of Shahin et al. (Infection and Immunity 1995, 63(4):1195-1200).

Claims 28 to 31, 33, and 35 stand rejected under 35 U.S.C. §103(a) as being obvious in view of the combination of Shahin et al. and O'Hagan (US 5,603,960).

Claims 38 and 41 stand rejected under 35 U.S.C. §103(a) as being obvious in view of the combination of Shahin et al. and Andrianov (US 5,807,757).

Claims 39 and 42 stand rejected under 35 U.S.C. §103(a) as being obvious in view of the combination of Shahin et al., O'Hagan, and Andrianov.

Applicant respectfully traverses the Examiner's rejections.

Discussion**Discussion of the §112, first paragraph (enablement), rejections**

Claims 21 to 25, 27 to 31, 33, 35, 38, 39, and 41 to 43 stand rejected under 35 U.S.C. §112, second paragraph, as failing to comply with the enablement requirement. Although not explicitly stated, applicant assumes that claims 44 and 45 also stand rejected as failing to comply

with the enablement requirement. The Examiner has asserted that specification is not enabling for methods of inducing a protective immune response using any antigen.

Applicants submit that the proper standard for a §112, first paragraph, enablement rejection is whether the application contains sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. MPEP §2164.01. Accordingly, the issue is whether one of skill in the art having the present specification before him could make and use the claimed invention without undue experimentation. With regard to providing a "protective immune response", the Examiner is directed to page 8, lines 24 to 27, which recites:

As used herein, the term "protective immunity" refers to at least 75% clearance, more preferably 90% clearance of the challenging agent, such as an infectious agent, from the subject preferably within 3 weeks after the introduction of the challenging agent, more preferably within 2 weeks, most preferably within days.

Accordingly, one of skill in the art having the present specification before him could make and use the claimed invention if he/she could determine if 75% clearance of a challenging agent (an antigen) has occurred. Such methods of determining clearance are exemplified in the specification (Examples 5 to 8). This is very different than the Examiner's assertion that the presently claimed invention requires "one of skill in the art to discover a method for curing HIV, cancer, herpes simplex 1, etc." (page 4 of the present action). The key to applicant's inventive contribution is the discovery of methods that provide 75% clearance of an antigen. Accordingly, given the guidance in the application as identified above and the level of skill in the art, applicant submits that the claimed invention would not require undue experimentation. As stated in the MPEP, section 2164.06:

"[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Given the guidance in the Specification, the Examples section of the application, and methods known in the art, one of ordinary skill in the art would be able to generate micro(nano)particles comprising any antigen and test them for their ability to induce an immune response resulting in 75% clearance of the antigen. If the Examiner chooses to maintain this rejection, applicants respectfully request that the Examiner explain which steps, such as preparing antigen, encapsulating antigen, orally administering the encapsulated antigen, and measuring clearance are beyond the abilities of the ordinary skilled artisan.

Accordingly, applicant respectfully requests that the rejection of claims 21 to 25, 27 to 31, 33, 35, 38, 39, 41 to 45 under 35 U.S.C. §112, first paragraph (enablement), be withdrawn.

Discussion of the Art Rejections: Section 103(a) - Obviousness

(A) The Rejections of Claims 23 to 25 and 27

Claims 23 to 25 and 27 stand rejected under 35 U.S.C. §103(a) as being obvious in view of Shahin et al. (Infection and Immunity 1995, 63(4):1195-1200).

Applicant respectfully traverses the rejection.

Claim 21 is directed to a method of inducing a protective immune response, requiring oral administration of a first and a second subpopulation of microparticles, wherein each of said microparticles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the microparticles of the first subpopulation is different than the antigen in the microparticles of the second subpopulation and at least 50% of the microparticles are less than 5 μ m. Claims 22 to 25 and 27 all depend from Claim 21.

Shahin et al. discloses the benefits of intranasal administration of the secreted *B. pertussis* proteins FHA, pertussis toxin, and pertactin. In regard to oral administration, Shahin et al. states that administration of microencapsulated FHA fails to stimulate “a protective mucosal response via the oral route” (Shahin et al., page 1199, col. 2, para. 2, lines 12 to 13). Shahin et al. also discloses that “less than 1% of an oral dose of DL-PLG microspheres successfully reaches the Peyer’s patch”, indicating that oral administration of microspheres is a poor route for inducing immunity (Shahin et al., page 1199, col. 2, para. 2,

lines 15 to 16). Furthermore, Shahin et al. states that “Respiratory immunization with antigens...has been a successful strategy for the induction of both systemic and mucosal immune responses” (Shahin et al., page 1199, col. 2, para. 3, lines 1 to 3). Accordingly, Shahin et al. teaches respiratory (intranasal) administration of vaccines because oral administration does not work.

The presentation of an obviousness rejection based on a single reference requires three steps: 1) providing a suggestion or motivation to modify the reference; 2) providing a reasonable expectation that the modification will be successful; and 3) providing a modification that teaches all of the claim limitations. Steps 1) and 2) must be found in the prior art.

MPEP §2143 states:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant submits that the Examiner has not satisfied any of these requirements.

MPEP §2141 states (emphasis added), “The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination”. In considering Shahin et al. in its entirety, it is clear that Shahin et al. teaches away from the use of oral administration and promotes the benefits of intranasal administration. The Examiner has asserted that one of skill in the art would have, upon reviewing Shahin et al., chosen to modify Shahin et al. to use the oral route. However, the Examiner provides no basis why one of skill in the art would discount the teachings of Shahin et al., which teaches exactly the opposite, that the intranasal route is superior. In presenting the rejection the cited reference must be read as a whole and it is improper to selectively ignore direct teachings away that would refute any basis to modify a reference. Applicant respectfully submits that the present obviousness rejection is based on a hindsight reconstruction of the present invention. As

noted above, the publication must be considered as a whole. The Examiner has presented no objective evidence that, without the present application to use a guide, one of skill in the art would, upon reviewing Shahin et al., have selectively ignored those portions of Shahin et al. that teach away from using oral administration. Without the present application, one of ordinary skill in the art would have no basis to selectively ignore those portions of Shahin et al. Applicant submits that one of ordinary skill in the art would 1) not modify a publication to contradict itself; and 2) not expect such a modification to be successful.

Applicant respectfully submits that the present obviousness rejection is based on a hindsight reconstruction of the present invention. As noted above, the publications must be considered as a whole. The Examiner has presented no objective evidence that, without the present application to use a guide, one of ordinary skill in the art would, upon reviewing Shahin et al., have selectively ignored those portions of Shahin et al. that discount the use of oral administration. Applicant submits that one of ordinary skill in the art would 1) not modify a publication that teaches away from using oral administration; and 2) not expect such a modification to be successful.

In view of the lack of a motivation to modify Shahin et al., and the lack of any expectation of success should such a modification be made, applicant respectfully requests the withdrawal of the rejections of Claims 21 to 25, and 27 under 35 U.S.C. §103(a).

Furthermore, even if the *prima facie* case of obviousness were to be established, applicant submits that the present invention is nonobvious in view of the objective evidence presented below.

MPEP §2141 states (emphasis added):

Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

As noted in previous replies, applicant respectfully submits that one of ordinary skill in the art would not consider the modification of Shahin et al. as a valid teaching that

administration of more than one antigen is more effective than administering a single antigen based upon the data of Shahin et al. Applicant submits the Examiner has not specifically addressed how the data of Shahin et al. supports the conclusory statements found in the abstract of Shahin et al. If the Examiner maintains this rejection, applicants respectfully request that the Examiner explain why the ordinary skilled artisan would follow the teachings of Shahin et al. given that these conclusions are not adequately supported by the data in Shahin et al.

To reiterate, the data is insufficient to support a teaching of administration of multiple antigens being more effective than administering only one antigen.

To illustrate why the data presented in Shahin et al. is confusing at best, the Examiner is respectfully directed to Table 7 on page 1199 of Shahin et al. which discloses the Log₁₀ CFU from the lungs and trachea of mice treated intranasally with different combinations of antigens. In particular, one of skill in the art upon reading this section would realize that critical data has been omitted. Results have only been shown for only 2 out of 7 (lungs) and 1 out of 7 (trachea) infected mice. In other terms, the results for 5 out of 7 mice (71%) and 6 out of 7 mice (86%) of the data was selectively not presented. In other experiments, the results for lungs and trachea, 60% and 80% of the data points, respectively, are not shown. The authors provide no explanation for their selective omission of up to 86% of the data for the other infected mice. Applicant respectfully submits that one of ordinary skill in the art would question to why the data from the other mice was omitted and accordingly would be skeptical as to the veracity of the data and the conclusions drawn therefrom. Applicant submits that the teaching of Table 7 is insufficient to support a teaching of more than one antigen being more effective than administering only one antigen.

In view of the weak data of Shahin et al., the disclosure of the present application demonstrates unexpected results (applicant's data, surprisingly, shows synergism), the satisfaction of a long felt need (improved vaccination), and failure of others (the data supporting the claims of Shahin et al. are very weak). In contrast to the data presented in Shahin et al., Figure 6 of the present application demonstrates, using all of their mice (see Example 7 on pages 20 to 21), that after 14 days, PT +FHA gives better than 2 Log₁₀ units improvement over PT alone. Accordingly, in view of the secondary considerations of long

felt need, failure of others, and unexpected results applicant submits that the claimed invention is nonobvious and respectfully requests the withdrawal of the rejection of claims 21 to 25, and 27 under 35 U.S.C. §103(a).

In addition, although the Examiner asserts that even though the oral administration performed by Shahin et al. did not work, "it would have been obvious to one of ordinary skill in the art at the time of the invention was made to administer a larger amount of the microcapsules the was used in the intranasal administration" (page 9 of the present action). Applicant notes that Shahin et al. actually did use larger amounts for oral administration, 100-fold larger (100 µg does for oral administration compared to 1 µg doses for intranasal administration; see page 1198, all of column 1), but still could not elicit an immune response via the oral route. Clearly this is an example of "failure by others".

In contrast, applicant has used the same 100 µg dose for oral administration (page 18, line 12; page 19, line 13; page 20, line 8; page 20, lines 20 to 24; page 21, lines 14 to 21) and have been successful in eliciting a protective immune response. Clearly, these results are unexpected in view of the oral administration data of Shahin et al. Accordingly, in view of the secondary considerations of failure of others and unexpected results, applicant submits that the claimed invention is nonobvious and respectfully requests the withdrawal of the rejection of claims 21 to 25, and 27 under 35 U.S.C. §103(a).

(B) The Rejections of Claims 28 to 31, 33, and 35

Claims 28 to 31, 33, and 35 stand rejected under 35 U.S.C. §103(a) as being obvious in view of the combination of Shahin et al. and O'Hagan et al. (US 5,603,960).

Applicant respectfully traverses the rejection.

Claim 28 covers a method of inducing a protective immune response, requiring oral administration of a first and a second subpopulation of microparticles, wherein each of said microparticles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the microparticles of the first subpopulation is different than the antigen in the microparticles of the second subpopulation and at least 50% of the microparticles are less than 600 nm. Claims 29 to 31, 33, and 35 all depend from Claim 28.

The incompatibility of the teachings of Shahin et al. with the proposed modification of Shahin et al. is discussed above. O'Hagan et al. has been applied for the teaching of a nanospheres with mean sizes of "about 500 nm" and "between 200 nm and 200 μ m", respectively. The teachings of O'Hagan do not provide any motivation to modify Shahin et al. Accordingly, these teachings provide no basis to overcome the deficiencies of Shahin et al.. Since O'Hagan et al. does not provide any information that overcomes the deficiencies in Shahin et al., applicant requests respectfully withdrawal of the obviousness rejection of Claims 28 to 31, 33, and 35 which besides Shahin et al., additionally relies on O'Hagan et al.

(C) The Rejections of Claims 38 and 41

Claims 38 and 41 stand rejected under 35 U.S.C. §103(a) as being obvious in view of the combination of Shahin et al. and Andrianov (US 5,807,757).

Applicant respectfully traverses the rejection.

Claims 38 and 41 cover the methods of Claims 21 and 23 wherein the microparticles in each subpopulation are formed by coacervation.

The incompatibility of the teachings of Shahin et al. with the proposed modification of Shahin et al. is discussed above. Andrianov has been applied for the teaching of a method for preparing polyphosphazene microspheres by coacervation. The teachings of Andrianov do not provide any motivation to modify Shahin et al. Accordingly, these teachings provide no basis to overcome the deficiencies of Shahin et al. Since Andrianov does not provide any information that overcomes the deficiencies in Shahin et al., applicant requests respectfully withdrawal of the obviousness rejection of Claims 38 and 41 which besides Shahin et al., additionally relies on Andrianov.

(D) The Rejections of Claims 39 and 42

Claims 39 and 42 stand rejected under 35 U.S.C. §103(a) as being obvious in view of the combination of Shahin et al., O'Hagan et al., and Andrianov.

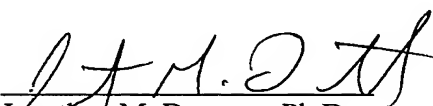
Applicant respectfully traverses the rejection.

Claims 39 and 42 cover the methods of claims 28 and 29 wherein the nanoparticles in each subpopulation are formed by coacervation.

The incompatibility of the teachings Shahin et al. with the proposed modification of Shahin et al. is discussed above. As noted above, since O'Hagan et al. and Andrianov do not provide any information that overcomes the deficiencies in Shahin et al., applicant requests respectfully withdrawal of the obviousness rejection of Claims 38 and 41 which besides Shahin et al., additionally relies on O'Hagan et al. and Andrianov.

Applicants submit that the present claims define allowable subject matter, and a prompt and favorable action is solicited respectfully.

Respectfully submitted,


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